8. Cardiac Function & Arrhythmias

Myocardial cells

- Sarcolemma: cell membrane
- Intercalated disk: gap junctions bet
- T-tubules: pathway for electrical impulses
- Sarcoplasmic reticulum: house intracellular Ca^{2+}
- Mitochondria: 35% of cell volume (typically relies on aerobic metabolism/maintain oxygen levels)

Myocytes ion movement and channels

- Ion movement across the membrane serves as the basis of the action potential
- Depends on two major factors
    - Energetics
        - Concentration gradient: diffusion from areas of higher concentration to lower concentration
        - Transmembrane potential (voltage): electrical potential of a cell exerts electrical force on ions (membrane potential -90mV)
    - Permeability
        - Phospholipid bilayer is not permeable to charged particles
        - Dependent upon specific voltage-gated ion channels

ECF		ICF	
$[Na^+]$	145mM	$[Na^+]$	15mM
$[K^+]$	5mM	$[K^+]$	150mM
$[Ca^{2+}]$	2mM	$[Ca^{2+}]$	0.2μM
$[Cl^-]$	120mM	$[Cl^-]$	5mM

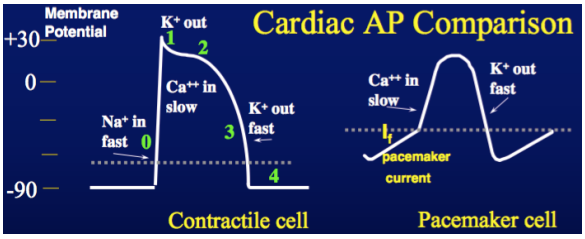
- Cardiac resting potential channels
    - Cardiac resting potential depends upon concentration gradient and which channels are open
    - Na^+/K^+/ATPase pump
        - Couples ATP hydrolysis to export 3 Na^+ outward and 2 K^+ inward
        - Causes cell to become more negative
    - K^+ channels
        - K^+ outward (down concentration gradient)
        - Causes cell to become more negative
        - However K^+ is attracted into cell as cell becomes more negative (therefore maintaining resting potential at -90mV)
- Cardiac action potential channels
    - As cell membrane potential is altered, its permeability to specific ions changes (channels become activated or inactivated)
    - Fast voltage-gated Na^+ channels
        - At -90mV channel is 'resting' (closed)
        - Rapid depolarization causes channel to open (-70mV)
        - Spontaneously change to inactive state (cannot re-open until return to -90mV)
    - L-type Ca^{2+} channels
    - K^+ channels
    - I_f (funny currents)

Cardiac action potential (contractile cells)

- Long duration (plateau phase allows for relaxation of myocytes)
- Self propagating
- Cell to cell (non-directional)
- Non-spontaneous
- Phases
    - Phase 0/Rapid depolarization: Most channels closed, membrane potential becomes less negative (via gap junctions) causing some Na^+ channels to open, membrane potential reaches 'threshold potential' (-70mV), many fast voltage-gated Na^+ channels open (Na^+ flows into the cell), rapid depolarization (membrane potential reaches +30mV)

- Phase 1/Brief reversal: Fast voltage-gated Na^+ channels close, some K^+ channels open (K^+ flows out of cell slowly), membrane potential is slightly reduced (towards 0mV)
- Phase 2/Plateau: L-type Ca^{2+} channels open (Ca^{2+} flows into cell slowly), some K^+ channels open (K^+ flows out of cell slowly), balance of positive charges flowing in and out of cell, longest phase of AP (note: Ca^{2+} inside cell plays a critical role in contraction -calcium induced calcium release-)
- Phase 3/Repolarization: Larger number of K^+ channels open (K^+ flows out of cell quickly), low membrane permeability for other ions, repolarization (membrane potential becomes more negative)
- Phase 4/Resting potential: membrane potential returns to -90mV

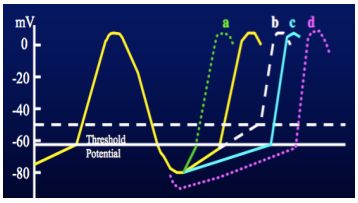
- Refractory period
  - Period during which a cardiac action potential (contractile cells) cannot be reinitiated until membrane potential returns to near resting
  - Long refractory period ensures forward propagation and protects the heart against tetanic contracture
  - Note: no hyperpolarization because only K^+ channels are open during phase 4/resting potential and its equilibrium is -90mV
  - Three refractory periods
    - Absolute RP: cell is completely unexcitable due to inactivity of fast voltage-gated Na^+ channels
    - Effective RP: cell can produce weak, localized AP, possible if a few fast voltage-gated Na^+ channels have returned to resting state and become excitable
    - Relative RP: cell can produce small, propagating AP (ectopic beats) since many fast voltage-gated Na^+ channels have returned to resting state and become excitable



Cardiac action potential (pacemaker cells)

- Automaticity (self-initiate depolarization in a rhythmic fashion)
- SA node/AV node
- Shape of pacemaker cell AP differs in three ways
  - Maximum voltage is -60mV
    - Less negative membrane voltage causes fast voltage-gated Na^+ channels to remain inactive
  - Phase 4 is not flat
    - Ionic flux, known as pacemaker current/funny current I_f, is open during repolarization (Na^+ moves into cell)
  - Phase 0 upstroke is less rapid
    - Fast voltage-gated Na^+ channels are inactive, therefore upstroke relies upon Ca^{2+} influx
- Phases
  - Phase 0/Depolarization: threshold is reached, Ca^{2+} channels open (Ca^{2+} inflow)
  - Phase 3/Repolarization: many K^+ channels open (rapid K^+ outflow)
  - Phase 4/Resting: as soon as -60mV membrane voltage is reached, pacemaker/funny current activates (slow Na^+ inflow)
- Latent pacemakers (AV node/bundle of his, purkinje fibers, etc.) are inactivated by native pacemakers (SA node)
  - Two mechanisms
    - Pre-empting: faster and earlier depolarization of SA node pre-empts and induces AP within AV node (via intercalated discs/gap junctions) before AV node threshold reached spontaneously
    - Overdrive suppression: more frequent depolarization of AV node than its native rate due to pre-empting leads to increased [Na^+] within the cell, causing Na^+/K^+ ATPase pump to increase activity, therefore leading to hyperpolarization and decreased excitability

- Latent pacemakers (AV node/terminal purkinje fibers) are inactivated by adjacent contractile cells
    - AV node is adjacent to atrial myocytes
    - Terminal purkinje fibers are adjacent to ventricular myocytes
    - Tendency for contractile cells to hyperpolarize nearby latent pacemakers (resting membrane potential of contractile cells is -90mV) therefore decrease excitability
- Impulse conduction
    - Propagation of electrical signal from one cardiac cell to another across gap junctions
    - Signal originates in SA node in right atrium (100 – 110 bpm native rate (slowed down by vagus nerve) → [note: interatrial tract (Bachmann's bundle) allows left atrium to synchronize with right atrium] → internodal tract → AV node (60 – 80bpm native rate) intrinsic rate, consists of small diameter fibers and inactive Na^+ channels leading to slow conduction, allows blood from atria to move into ventricles before ventricles contract) → bundle of His → left/right bundle branches (line walls of ventricular septum) → purkinje fibers (30 – 40bpm native rate, line walls of ventricles, high density of Na^+ channels leading to rapid conduction)
- Heart rate (HR)

	Increase	Decrease
Slope of I_f	(a) - Increased HR (positive chronotropic effect) - Time required to reach threshold potential decreased - Substances that increase permeability of Ca^{2+} and Na^+ - I.e. Noradrenaline and Adrenaline - SNS	(c) - Decreased HR (negative chronotropic effect) - Time required to reach threshold potential increased - PSNS
Maximum negative diastolic potential	(d) - Decrease HR (negative chronotropic effect) - Substances that increase K^+ permeability (hyperpolarize resting membrane potential) - I.e. Acetylcholine (increased K^+ and decreased Ca^{2+}/Na^+) - PSNS	
Threshold potential	(b) - Decreased HR (negative chronotropic effect) - I_f must work harder to reach threshold potential - PSNS	

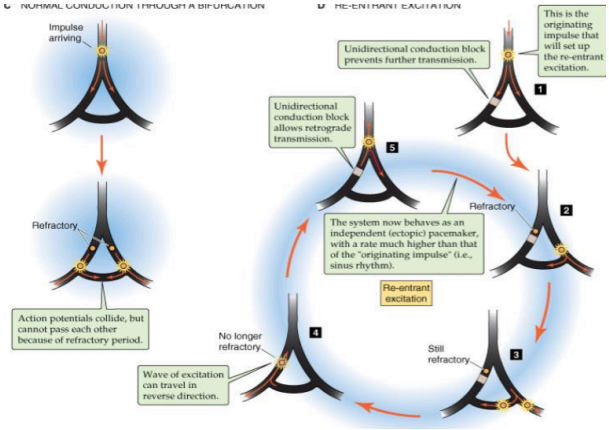
Excitation – contraction coupling

- Converting electrical AP into mechanical work via ATP
- Pacemaker cells → contractile cells (excitation) → contractile cells (contraction)
- Initiation: during phase 2/plateau of cardiac action potential (contractile cells) Ca^{2+} enters cardiac myocytes → increased $[Ca^{2+}]$ leads to Ca^{2+} induced Ca^{2+} release from sarcoplasmic reticulum → Ca^{2+} activates actin-myosin cross bridges → sliding filaments are pulled past each other and myocytes shortens (contraction)
- Termination: Ca^{2+} is moved into ECF or actively re-up taken into the sarcoplasmic reticulum and stored → cross bridge uncoupling → sliding filaments passively return to original position (relaxation)

ECG abnormalities and cardiac arrhythmias

- Consequences of cardiac arrhythmias
    - Atrial fibrillation: stagnation (blood remains in atria → reverse blood flow), higher venous pressure, asynchronous ventricular activation
    - Ventricular tachycardia: limited passive filling time, blood pressure and cardiac output drop (low forward blood flow)
    - Ventricular fibrillation: total cessation of effective pumping (no forward blood flow)
- Origins of cardiac arrhythmias
    - Abnormal impulse generation: automatic mechanisms, triggered activity
    - Abnormal impulse conduction: slowed conduction, unidirectional block and re-entry
- Mechanisms of cardiac arrhythmias

- Automatic mechanisms (abnormal pacemaker activity)
  - Occur when latent pacemaker cells override native pacemaker cells
  - Escape beats
    - Delayed
  - Ectopic beats (PAC/PVC)
    - Premature
    - Post-extrasystolic potentiation (following ectopic beats)
      - Extrasystole = premature beat
      - Premature beat had less time for ventricular filling, therefore had less contractile force (Frank-Starling law)
      - During compensatory pause Ca^{2+} leaks out of sarcoplasmic reticulum and into cytosol → Bowditch effect (increased $[Ca^{2+}]$ = increased contractility of following beat)
      - Note: compensatory pause also leads to increased filling time, therefore increased EDV, stretch and systolic pressure
- Triggered activity
  - Abnormal action potentials are triggered by a preceding action potential resulting in after-depolarization
  - Early afterdepolarization: occurs during phase 2 or early phase 3 (remains relatively local due to inactive fast voltage-gated Na^+ channels)
  - Delayed afterdepolarization: occurs during late phase 3 or phase 4 (propagates to adjacent cells due to resetting of fast voltage-gated Na^+ channels)
- Heart block (transient or permanent)
  - Caused by ischemia, fibrosis, trauma
  - Commonly AV block
  - Will generate escape beat/rhythm (occur in the seconds after impulse fails to reach ventricles)
- Re-entry
  - For re-entry to occur, closed loop, unidirectional block and slow conduction must be present



- Electrolyte imbalances underlying lethal ventricular arrhythmias
  - Increased extracellular $[K^+]$
    - Caused by ischemia
    - Less negative membrane potential (less K^+ will flow out of cell down its concentration gradient)
    - Less fast voltage-gated Na^+ channels open (due to less negative membrane potential) → phase 0/depolarization less rapid/steep → slowed conduction velocity (QRS widens) → decreased excitability (leads to unidirectional block)→ re-entry and bradycardia
    - Increased distance to threshold and delay repolarization/plateau of AP
  - Decreased extracellular $[K^+]$
    - Caused by starvation, anorexia, bulimia or diuretics
    - More negative membrane potential (more K^+ will flow out of cell down its concentration gradient)
    - More fast voltage-gated Na^+ channels open (due to more negative membrane potential) → phase 0/depolarization is more rapid/steep → increased conduction velocity → increase excitability → ventricular tachycardia or fibrillation
    - Decrease distance to threshold and shorten repolarization/plateau of AP
  - Increased intracellular $[Ca^{2+}]$
    - Caused by glycosides (prevent Ca^{2+} removal), catecholamines and ischemia
    - Lead to oscillatory after-potentials (via Ca^{2+} induced Ca^{2+} release) → arrhythmias